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For and on behalf of RWS Group Ltd

The 5th day of January 2009

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21. December 2007 TM/CG/mh

Description

Pharmaceutical Composition for Prevention and/or Symptomatic Treatment of Cystic Fibrosis

The present invention concerns a pharmaceutical composition for prevention and/or symptomatic treatment of cystic fibrosis, a corresponding application aid, a corresponding kit and use of the pharmaceutical composition.

Infections with pseudomonads, especially *Pseudomonas aeruginosa*, represent a serious clinical problem, especially in patients with immune suppressions, serious trauma and burns. The lethality of bacteriemias caused by *Pseudomonas aeruginosa* is about 20%. If pneumonia or a surgical complication is additionally present, the mortality rate in this type of bacteriamia can even rise to 30 to 50%. The clinical significance of *Pseudomonas aeruginosa* is especially clarified by the fact that this type of pseudomonad plays a critical role in about 40% of all deaths of patients with inhalation-induced pneumonia.

The most important clinical significance of *Pseudomonas aeruginosa* is in patients with cystic fibrosis (mucoviscidosis). Cystic fibrosis or mucoviscidosis is a genetically-related, autosomal-recessive congenital metabolic disease. It is due to a mutation of the gene for the chloride ion channel CFTR (Cystic Fibrosis Transmembrane Conductance Regulator). The genetic defect of the CFTR protein leads to different clinical problems, especially pulmonary and gastrointestinal symptoms. From a clinical standpoint, mostly the pulmonary symptoms are problematical. In almost all patients, chronic pneumonia with pseudomads occurs during cystic fibrosis, especially *Pseudomonas aeruginosa*, which represents the main reason for destruction of the lung and premature death of these patients. Cystic fibrosis, at least in the European Union and the USA, represents the most common autosomal-recessive hereditary disease. With a rate of one affected child per 2,500 births, in the EU alone, about 40,000 children and young adults per year suffer from cystic fibrosis.

The applicability of different antidepressants to prevent and/or treat certain infectious diseases is described in In WO 2004/017949 A2. The use of amitriptyline and imipramine for systemic treatment of viral infections is described there, in particular.

In order to improve prevention, and especially symptomatic treatment of cystic fibrosis, and especially to take into account the problems known from the prior art in this respect, the invention sets itself the task of providing a pharmaceutical composition that is particularly suited for prevention and systematic treatment of cystic fibrosis. The invention also sets itself the task of providing a corresponding application aid, as well as corresponding kit.

This task is solved according to the invention by a pharmaceutical composition for prevention and/or symptomatic treatment of cystic fibrosis, especially for prevention and/or treatment of infections occurring in cystic fibrosis and/or infectious diseases, including at least an antidepressant and at least a dispersant.

The invention is based, among other things, on the surprising finding that accumulation of ceramide occurs in the lung epithelial cells of mice, who do not express Cftr (Cystic Fibrosis Transmembrane Conductance Regulator) in the lung. In the case of Cftr, the mouse equivalent of CFTR is involved, for which reason mice that do not express Cftr (so-called Cftr-knockout mice), represent appropriate model organisms for cystic fibrosis. The rise in ceramide concentration in the epithelial cells of the lungs is then due especially to a rise in pH value (alkalization) in intracellular vesicles. Because of the rise in intravesicular pH value, the ceramide-degrading enzyme acid ceramidase is more strongly inhibited than the ceramide-releasing enzyme acid sphingomyelinase. This disequilibrium with reference to inhibition of acid ceramidase and acid sphingomyelinase causes accumulation or enrichment of ceramide in the intracellular vesicles of lung epithelial cells. Ceramide accumulation finally leads to cell death of the epithelial cells. If the cells die off, cell components, especially DNA, reach the bronchial lumen. Pathogens present in the lung, especially pseudomads, can adhere to these cell components. Microbial population or colonization of the lung is promoted on this account, so that the risk that the initially mentioned pulmonary symptoms of cystic fibrosis will manifest themselves in the affected patients increases.

In the context of the invention, it could be interestingly demonstrated by means of Cftr-deficient mice (Cftr-knockout mice) that the composition according to the invention causes stronger inhibition of acid sphingomyelinase than acid ceramidase, especially during intrapulmonary, pref-

erably inhalative administration. It could also be demonstrated that the composition according to the invention led to normalization of ceramide concentration in the lung epithelial cells of experimental animals. It could also be demonstrated with particular advantage that, after administration of the composition according to the invention, the vulnerability to infection of the experimental animals also normalized.

In a preferred variant, the antidepressant is dispersed in a dispersant. The dispersant is preferably liquid. The dispersant, with particular advantage, represents an aqueous liquid, especially a physiological liquid. For example, the dispersant can be a physiological buffer or salt solution.

The composition according to the invention can be present, in principle, in the form of a pharmaceutical formulation. The formulation can occur in the gaseous, liquid, semisolid or solid state. The composition can be present accordingly as an aerosol, dispersion, gel, paste, salve, tablet or powder. The composition is preferably present in the form of a liquid formulation. The composition can be present, in particular, in the form of an aqueous dispersion, preferably an aqueous solution. The composition can be present, for example, as a nasal or oral spray or drop solution. The composition according to the invention is preferably present as an oral spray or inhalate.

The composition can contain especially additional additives, for example, binders, softeners, diluents, vehicles, lubricants, antistatic agents, antioxidants, adsorption agents, separating agents, dispersants, tablet coating, defoaming agents, film-forming agents, emulsifiers, extenders and/or fillers. If present in liquid form, the composition can contain flavor enhancers, preservatives, stabilizers and/or buffers.

The aforementioned additives can consist of organic and/or inorganic additives, for example, water, sugar, salts, acids, bases, alcohols, organic polymer compounds and the like. Preferred sugars are glucose, lactose and/or fructose. An example of appropriate salt is table salt, which is ordinarily used in the form of a table salt solution.

The pharmaceutical composition is proposed in another variant for parenteral administration. In principle, all forms of administration known to one skilled in the art that avoid the gastrointestinal tract are considered as parenteral forms of administration. For example, the composition can be proposed for intravenous and/or intra-arterial administration. The composition is preferably proposed for intrapulmonary, especially inhalative, administration. It could be demonstrated, with particular advantage, that the composition for intrapulmonary, especially inhalative, prevention and/or symptomatic treatment or therapy need have significantly lower amounts or doses of the antidepressant than, for example, during intravenous administration, in order to achieve a comparable prophylactic or therapeutic effect. This is especially true with respect to activity of acid sphingomyelinase, ceramide concentration and vulnerability to infection. Thus, a composition provided for intrapulmonary administration, especially in the form of an inhalation agent, can contain the antidepressant in a dose that corresponds to about 1/100 of the dose prescribed for intravenous administration, for example, in the form of an injection solution. In the case of intrapulmonary, especially inhalative, administration, undesired side effects of the antidepressant, for example, fatigue and sleepiness, can largely be eliminated.

The antidepressant itself can be a tri- and/or tetracyclic antidepressant. The antidepressant is preferably a tricyclic antidepressant. It is especially prescribed according to the invention that the antidepressant is a dibenzazepine derivative, especially a derivative of 10,11-dihydro-5H-dibenz[b,f]azepine.

In a further variant, the antidepressant is chosen from the group imipramine, amitriptyline, amitriptyline oxide, chlomipramine, desipramine, trimipramine, lofepramine, nortriptyline, dibenzepine, opipramole, maprotiline, doxepine and their combinations. The antidepressant, with particular preference, is amitriptyline and/or a derivative derived from it, especially an antidepressant of the amitryptiline type. In another variant, the antidepressant is fluoxetine and/or a derivative thereof. It can be prescribed according to the invention, in particular, that the antidepressant be present in the form of a physiologically compatible salt, especially in the form of a hydrochloride.

In another advantageous variant, the pharmaceutical composition, in addition to the antidepressant, contains at least one other therapeutically active ingredient. The active ingredient can be chosen from the group β-cyclodextrin, nystatin, filipin and antibodies. The antibodies are usually antibodies directed against acid sphingomyelinase.

As already mentioned, the composition according to the invention is especially suited for prevention or symptomatic treatment of infections or infectious diseases that occur in cystic fibrosis. The infections or infectious diseases can be caused at least by one of the pathogens from the group *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Staphylococcus aureus* and *Haemophilus influenzae*.

In a preferred variant, the pharmaceutical composition is assigned to an application aid, especially an inhalator. Preferably, the pharmaceutical composition is contained in an application aid. The application aid can be a spray device, as are ordinarily available in pharmacies. The application aid itself, with particular advantage, has a mouthpiece, a nebulizer and a pump.

Another aspect of the invention concerns an application aid, especially an inhaler, which contains the composition according to the invention. The previous description is referred to concerning features and details of the application aid.

The invention also includes a kit for prevention and/or systematic treatment of cystic fibrosis, especially for prevention and/or treatment of infections and/or infectious diseases occurring in cystic fibrosis, in which the kit includes at least one antidepressant and at least one dispersant. The kit can contain a buffer solution as additional component. The antidepressant and the dispersant are preferably contained together in a container. The container can be designed, in particular, as an application aid for administration of the antidepressant and the dispersant. It can also be prescribed according to the invention that the antidepressant and the dispersant be present separate from each other in the kit. In this variant, the antidepressant can be present in powder or tablet form. With reference to additional features and details concerning the kit, especially the antidepressant, dispersant and application aid, the previous description is referred to.

The present invention also concerns the use of the composition according to the invention to produce a drug or medication for prevention and/or symptomatic treatment of cystic fibrosis, especially for prevention and/or treatment of infections and/or infectious diseases occurring during cystic fibrosis. The previous description is referred to for additional features and details.

Finally, the invention also concerns a method for prevention and/or systematic treatment of cystic fibrosis, especially for prevention and/or treatment of infections and/or infectious diseases occurring in cystic fibrosis, in which the composition according to the invention is adminis-

tered, especially in a therapeutically effective amount. The previous description is also referred to concerning additional features and details.

The mentioned features and additional features of the invention are apparent from the following description of examples in conjunction with the dependent claims and figures. The individual figures can be implemented by themselves or in combination with each other. The figures are a content of the description by explicit reference.

In the figures:

Figure 1: schematically shows the activity of acid sphingomyelinase in wild-type mice and Cftr-deficient mice as a function of different forms of administration,

Figure 2: schematically depicts the ceramide concentration in wild-type mice and Cftr-deficient mice as a function of different forms of administration,

Figure 3: shows the vulnerability to infection in wild-type mice and Cftr-deficient mice as a function of different forms of administration.

1. Methods

1.1 Cftr-deficient mice

The Cftr-deficient mice were originally obtained from Jackson Laboratories (Bar Harbour, Maine, USA) and then raised at the Cycnad Company itself. The employed mice were deficient relative to Cftr. This is the mouse equivalent of human CFTR. The employed experimental animals, however, expressed the human CFTR in the intestine. This was

achieved under the control of a promoter for fatty acid-binding protein (FABP). This promoter mediates a specific intestinal expression of CFTR. The employed mice had a mixed genetic background, consisting of C57BL/6, FVB/N and 129.

To produce additional Cftr-knockout mice, gene-equivalent mice were used with reference to B6.129P2(CF/3)-$Cftr^{TgH(neoim)Hgu}$ (abbreviated: $Cftr^{MHH}$). The CF strain CF/3-$Cftr^{TgH(neoim)Hgu}$ produced by inbreeding was raised by strict pairing of brother and sister animals, starting from a mutated mouse of the original type $Cftr^{TgH(neoim)Hgu}$. The latter was produced by a so-called insertion mutagenesis in the Cftr-Exon10. The mouse produced small amounts of Cftr.

A gene-equivalent strain of the type $Cftr^{MHH}$ was also produced by back-crossing of the target mutation into the background B6 produced by inbreeding. Gene-identical B6 mice were then used as control animals. The hygienic state of the experimental animals was regularly checked according to the recommendations of FELASA, issued in 2002 (Federation of European Laboratory Animal Science Associations).

1.2 Determination of Activity of Acid Sphingomyelinase

The lungs of untreated mice and mice treated with amitriptyline were homogenized in a buffer of 250 mN sodium acetate (pH 5.0), 1.3 mM EDTA and 1% NP40, using a homogenizer. The homogenizate was subjected to a total of three ultrasonic treatments (ultrasonic processor tip sonicator). An aliquot of the samples was then diluted with 250 mM sodium aceate (pH 5.0) and 1.3 mM EDTA to 0.1% NP40 and incubated with a 0.05 μCi sample of [^{14}C] sphingomyelin (52 μCi/mmol; MP Biomedicals, Irvine, CA, USA). The radioactive sample of [^{14}C] sphingomyelin was dried, resuspended in 250 mM sodium acetate (pH 5.0), 1.3 mM EDTA and 0.1% NP40 and then subjected for 10 minutes to ultrasound treatment, before being added to the homogenized samples. The

samples were incubated for a total of 30 minutes at about 37°C. The enzymatic reaction was then ended by extraction (extraction with a solvent mixture of chloroform and methanol in a volume ratio chloroform/methanol of 2:1. The samples were then centrifuged and an aliquot of the aqueous phase subjected to scintillation counting, in order to determine release of [^{14}C] phosphorylcholine from [^{14}C] sphingomyelin.

1.3 Measurement of Ceramide Concentration

After killing of the experimental animals, the lungs were removed, 1mL of a mixture of chloroform, methanol and 1N HCl (100:100:1, v/v/v) was added, and then homogenized in a Dounce homogenizer three times for 20 seconds. After addition of 200 µL H_2O, the samples were centrifuged for 5 minutes (14,000 rpm). The lower phase was then collected, dried and subjected to alkaline hydrolysis in 0.1 N methanolic KOH at 37°C for 60 minutes. The samples were extracted again, the lower phase dried and then resuspended in 20 µL of a detergent solution (7.5% (w/v) n-octylglucopyranoside, 5 mM cardiolipin in 1 mM diethylenetriaminepentaacetic acid (DTPA)). After ultrasound treatment (10 minutes), the samples were added to 70 µL of a reaction mixture, containing 10 µL diacylglycerol kinase (GE Healthcare Europe, Munich, Germany), 0.1 M imidazo/ HCl (pH 6.6), 0.2 mM diethylenetriaminepentaacetic acid (pH 6.6), 70 mM sodium chloride, 17 mM magnesium chloride, 1.4 mM EGTA, 2 mM DTT, 1 µM ATP and 10 µCi [^{32}P]γATP. The kinase reaction was conducted for 30 minutes at room temperature and then stopped by adding 1 mL chloroform : methanol : 1 N HCl (100:100:1, v/v/v), 170 µl buffered salt solution (135 mM sodium chloride, 1.5 mM calcium chloride, 0.5 mM magnesium chloride, 5.6 mM glucose, 10 mM HEPES, pH 7.2) and 30 µl of a 100 mM EDTA solution. The samples were then vortexed and the formed phases separated. The lower phase was collected, dried, dissolved in 20 µL of a chloroform/methanol mixture (1:1, v/v) and separated by thin-layer chromatography (silica G 60 TLC plates, chloroform:methanol:acetic acid (65:15:5, v/v/v)). The thin-

layer chromatography plates were then covered with x-ray film. The ceramide spots were identified by means of comigration of a C_{16}-ceramide standard. Incorporation of [^{32}P] in ceramide was quantified by liquid scintillation counting after the spots had disappeared from the plates. The ceramide amounts were determined by comparison with a standard curve, using C_{16}-ceramide as substrate.

2. Experiments

Wild-type mouse and Cftr-deficient mice were inhaled with 1 mL of an amitriptyline solution (4 mg/L H_2O) for 20 minutes by means of an ordinary pharmacy inhalation device. The actually administered amount of amitriptyline was therefore about 4 µg. Parallel with this, other wild-type mice and Cftr-deficient mice were administered 100 µL of an amitriptyline solution (2.5 g/l H_2O) by injection, so that the actually administered amount of amitriptyline in these animals was 250 µg. The injections were administered twice a day for 2 days.

In the case of inhalative treatment, the lungs of the mice were extracted 60 minutes or 12 hours after the end of inhalation, in which, in 12 cases of 12-hour experiments, the inhalation was repeated after 6 hours. In the case of mice treated by the injection solution, their lungs were removed 12 hours after the last injection.

The lung extracts were investigated for activity of acid sphingomyelinase, ceramide concentration and occupation by *Pseudomonas aeruginosa*.

The following results were then specifically obtained:

<u>2.1 Acid Sphingomyelinase Activity</u>

An enzyme activity of 405 ± 19 pmol/min/mg of protein was found in the lung extracts of the untreated wild-type mice. The lung extracts of the untreated Cftr-deficient mice showed an enzyme activity of 375 ± 19 pmol/min/mg.

In the lungs extracted after 60 minutes of the wild-type mice treated by inhalation, an activity of 176 ± 18 pmol/min/mg of protein was found. In the lung extracts of the correspondingly treated Cftr-deficient mice, an enzyme activity of 148 ± 17 pmol/min/mg of protein was measured.

The lungs of the inhalatively treated wild-type mice, extracted after 12 hours, showed an enzyme activity of 200 ± 14 pmol/min/mg of protein. The lung extracts of the correspondingly treated Cftr-deficient mice showed an enzyme activity of 167 ± 9 pmol/min/mg of protein.

The lungs of the wild-type mice treated by injection solution showed an enzyme activity of 168 ± 19 pmol/min/mg of protein. The lung extracts of the correspondingly treated Cftr-deficient mice showed an enzyme activity of 151 ± 17 pmol/min/mg of protein.

These results are schematically shown in Figure 1. The activity of acid sphingomyelinase, measured in pmol/min/mg of protein, is plotted there on the ordinate. The wild-type and Cftr-deficient mice, as well as the different forms of administration, are shown on the abscissa. On the abscissa, the numbers mean:

1: Wild-type mice, untreated;

2: Cftr-deficient mice, untreated;

3: Wild-type mice, activity of acid sphingomyelinase 60 minutes after inhalation of 1 mL of an amitriptyline solution (4 mg/L);

4: Cftr-deficient mice, activity of acid sphingomyelinase 60 min after inhalation of 1 mL of an amitriptyline solution (4 mg/L);

5: Wild-type mice, activity of acid sphingomyelinase 12 h after inhalation of a 1mL of an amitriptyline solution (4 mg/L);

6: Cftr-deficient mice, activity of acid sphingomyelinase 12 h after inhalation of 1 mL of an amitriptyline solution (4 mg/L);

7: Wild-type mice, activity of acid sphingomyelinase 12 h after intraperitoneal injection of 250 µg amitriptyline;

8: Cftr-deficient mice, activity of acid sphingomyelinase 12 h after intraperitoneal injection of 250 µg amitriptyline.

Figure 1 clearly shows that the composition according to the invention, in the presence of cystic fibrosis, causes a significant inhibition of acid sphingomyelinase with particular advantage. The results show, in particular, that inhibition of ceramide-releasing enzyme can amount to between 55 and 66%, referred to the total cellular activity of acid sphingomyelinase in a Cftr-deficient mouse. In the case of inhalative administration of the composition according to the invention, it is also advantageous that this effect can already be achieved with low amitriptyline doses (effectively administered dose of amitriptyline in inhalative administration was 4 µg). Undesired side effects that usually occur with increasing amitryptiline doses can therefore be avoided.

<u>2.2 Ceramide Concentration:</u>

In the lung extracts of untreated wild-type mice, a ceramide concentration of 2.3 ± 0.5 pmol/µg of protein could be measured. The lung extracts of untreated Cftr-deficient mice showed a ceramide concentration of 16 ± 1.6 pmol/µg of protein.

In the lungs of wild-type mice, extracted after 12 h, a ceramide concentration of 1.6 ± 0.3 pmol/µg of protein was measured. The lung extracts of correspondingly treated Cftr-deficient mice showed a ceramide concentration of 5.2 ± 0.79 pmol/ µg of protein.

The lung extracts of wild-type mice treated by injection showed a ceramide concentration of 1.5 ± 0.4 pmol/µg of protein. The ceramide concentration in the lung extracts of correspondingly treated Cftr-deficient mice was 4.9 ± 0.7 pmol/µg of protein.

The results presented above are schematically shown in Figure 2. The ceramide concentration, measured in pmol/µg of lung protein, is shown on the ordinate. The wild-type and Cftr-deficient mice, including the different forms of administration, are shown on the abscissa. The numbers on the abscissa mean:

1: Wild-type mice, untreated;
2: Cftr-deficient mice, untreated;
3: Wild-type mice, ceramide concentration 12 h after inhalation of 1 mL of an amitriptyline solution (4 mg/L);
4: Cftr-deficient mice, ceramide concentration 12 h after inhalation of 1 mL of an amitriptyline solution (4 mg/L);
5: Wild-type mice, ceramide concentration 12 h after intraperitoneal injection 250 µg amitriptyline;
6: Cftr-deficient mice, ceramide concentration 12 h after intraperitoneal injection 250 µg amitriptyline.

It is clearly apparent from Figure 2 that the composition according to the invention is particularly suited of normalizing ceramide concentration in lung epithelium in the presence of cystic fibrosis. With reference to additional advantages, the comments under 2.1 are referred to.

<u>2.3 Measurement of Vulnerability to Infection for Pseudomonas aeruginosa</u>

In these experiments, wild-type mice and Cftr-deficient mice received, after 2-fold inhalation with 1 mL of an amitriptyline solution (4 mg/L H_2O), 1 x 10^8 CFU (colony forming units) of *Pseudomonas aeruginosa* Strain

762 in the nose. Untreated mice served as controls. The mice were killed 2 hours after application. The number of bacteria in the lung was then measured as a gauge of the sensitivity of the mice to *Pseudomonas aeruginosa* infection. For this purpose, the lungs were removed, mechanically homogenized, intracellular bacteria released by 10 minutes of treatment with 5 mg/mL saponin at 37°C, the samples washed with 10 mL PBS (phosphate buffered saline), the pellets taken up in PBS and aliquots plated on the TSA-agar plates. The bacterial colonies were counted after 15 hours of growth at 37°C as a gauge of the number of pulmonary bacteria and therefore as a gauge of infection. The following results were obtained:

In the lungs of untreated wild-type mice, a bacterial count of 4700 ± 2160 CFU could be measured. The removed lungs of the untreated Cftr-deficient mice showed a number of bacteria of $6.3 \times 10^6 \pm 1.87 \times 10^6$ CFU. The lungs of the wild-type mice treated by inhalation showed a bacterial count of 3600 ± 2892 CFU. In the lungs of Cftr-deficient mice treated by inhalation, a bacterial count of 12300 ± 4075 CFU could be established. The lungs of wild-type mice treated by the injection solution showed a bacterial count of 2780 ± 1740 CFU. The lungs of the correspondingly treated Cftr-deficient mice showed a bacterial count of 11250 ± 2360 CFU.

The aforementioned results are shown graphically in Figure 3. The number of bacteria (CFU – colony-forming units) measured in one gram of lung, as plotted on the ordinate. The untreated and treated wild-type mice and Cftr-deficient mice, including the different forms of administration, are shown on the abscissa. On the abscissa, the numbers mean:

1: Wild-type mice, bacterial count in the lungs 2 h after intranasal injection, no further treatment;

2: Cftr-deficient mice, bacterial count in the lungs 2 h after intranasal injection, no further treatment;

3: Wild-type mice, bacterial count in the lungs 12 h after inhalation of 1 mL of an amitriptyline solution (4 mg/L) and 2 hours after intranasal infection;

4: Cftr-deficient mice, bacterial count in the lungs 12 h after inhalation of 1 mL of an amitriptyline solution (4 mg/l) and 2 hours after intranasal infection;

5: Wild-type mice, bacterial count in the lungs 12 h after intraperitoneal injection of 250 μg amitriptyline and 2 hours after intranasal infection;

6: Cftr-deficient mice, bacterial count in the lungs 12 h after intraperitoneal injection of 250 μg amitriptyline and 2 hours after intranasal infection.

It is clearly apparent from Figure 3 that administration of the composition according to the invention leads to essential normalization of vulnerability to infection with *Pseudomonas aeruginosa*. Figure 3 especially shows a suitability of the composition according to the invention for prevention and/or treatment of infections or infectious diseases that occur in conjunction with cystic fibrosis. The comments already made under 2.1 are also referred to relative to additional advantages.

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Claims

1. Pharmaceutical composition for prevention and/or symptomatic treatment of cystic fibrosis, especially for prevention and/or treatment of infections and/or infectious diseases occurring in cystic fibrosis, comprising at least one antidepressant and at least one dispersant.

2. Pharmaceutical composition according to Claim 1, characterized by the fact that the antidepressant is present dispersed in a dispersant.

3. Pharmaceutical composition according to Claim 1 or 2, characterized by the fact that the dispersant is liquid.

4. Pharmaceutical composition according to one of the preceding claims, characterized by the fact that the dispersant is an aqueous liquid, especially a physiological liquid.

5. Pharmaceutical composition according to one of the preceding claims, characterized by the fact that it is present in the form of a preferably liquid formulation.

6. Pharmaceutical composition according to one of the preceding claims, characterized by the fact that it is present in the form of an aqueous dispersion, especially aqueous solution.

7. Pharmaceutical composition according to one of the preceding claims, characterized by the fact that it is proposed for parenteral, especially intrapulmonary, preferably inhalative, administration.

8. Pharmaceutical composition according to one of the preceding claims, characterized by the fact that the antidepressant is a tri- or tetracyclic antidepressant, preferably tricyclic.

9. Pharmaceutical composition according to one of the preceding claims, characterized by the fact that the antidepressant is a dibenzazepine derivative, especially a derivative of 10,11-dihydro-5*H*-dibenz[b,f]azepine.

10. Pharmaceutical composition according to one of the preceding claims, characterized by the fact that the antidepressant is chosen from the group imipramine, amitriptyline, amitriptyline oxide, chlomipramine, desipramine, trimipramine, lofepramine, nortriptyline, dibenzepine, opipramole, maprotiline, doxepine and their combinations.

11. Pharmaceutical composition according to one of the Claims characterized by the fact that the antidepressant is amitriptyline or a derivative derived from it.

12. Pharmaceutical composition according to one of the preceding claims, characterized by the fact that the composition, in addition to the antidepressant, has at least one additional therapeutic agent, chosen especially from the group β-cyclodextrin, nystatin, filipin and antibodies.

13. Pharmaceutical composition according to one of the preceding claims, characterized by the fact that the infections or infectious diseases are caused at least by one pathogen from the group *Pseudomonas aeruginosa, Staphylococcus aureus, Burkholderia cepacia* and *Haemophilus influenzae*.

14. Pharmaceutical composition according to one of the preceding claims, characterized by the fact that it is assigned an application aid, especially an inhalator, preferably contained in an application aid.

15. Application aid, especially inhalator, containing a pharmaceutical composition according to one of the Claims 1 to 13.

16. Kit for prevention and/or symptomatic treatment of cystic fibrosis, especially for prevention and/or treatment of infections and/or infectious diseases occurring in cystic fibrosis, comprising at least one antidepressant and at least one dispersant, according to at least one of the features of the characterizing part of Claims 2 to 14.

17. Kit according to Claim 16, characterized by the fact that the antidepressant and dispersant are together contained in a container.

18. Kit according to Claim 16, characterized by the fact that the antidepressant and dispersant are essentially present separate from each other.

19. Use of a pharmaceutical composition according to one of the Claims 1 to 14 for production of a drug or medication for prevention and/or symptomatic treatment of cystic fibrosis, especially for prevention and/or treatment of infections and/or infectious diseases occurring in cystic fibrosis.

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Summary

The invention concerns a pharmaceutical composition for prevention and/or symptomatic treatment of cystic fibrosis, especially for prevention and/or treatment of infections and/or infectious diseases occurring in cystic fibrosis, comprising at least one antidepressant and at least one dispersant.

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